REMARKS

Status of the Claims

Claims 1-31 are pending. Claims 23-31 were withdrawn from consideration by the Examiner. Claims 1-22 were rejected. Claim 18 was deemed allowable but objected to for depending from a rejected claim (see Office Action dated November 21, 2007). Applicants thank the Examiner for withdrawing the previously asserted claim rejection under 35 U.S.C. § 102(b) as being anticipated by Palomäki. See Office Action, page 7.

Amendments to the Specification

The specification was amended to make a minor improvement to the language in paragraph [018]. The specification was also amended to add "i.e. at time T2" in paragraph [070] to clarify that time of the second measurement is called time T2. This amendment finds support in the paragraph itself and in many other sections throughout the specification which discuss the two measurements at times T1 and T2 (see also remarks below). Paragraph [070] was also amended to add "-R3-L2 (or [...])" in the context of the L2-containing binding complexes that are being measured at time T2. The mention of the -R3-L2 containing binding complex was inadvertently omitted in the original paragraph [070]. The amendment is supported by the paragraph itself which earlier states that R3-L2 (or R3-X) is included in the reaction mixture ("solid phase-R1, analyte ("A"; provided it is present in the sample), R2-L1 and R3-L2 (or R3-X) are mixed together"). Correspondingly, the measurement of the L2-dependent signal relates to a solid phase-R1-analyte-R3-L2 (or -R3-X-Y-L2) binding complex. Consequently, none of the amendments adds new matter.

Objection to the Specification

The Office objected to the disclosure because of an alleged informality. Office Action, page 2. The Office requires a clarification why "sample" is used in the standard assay described in paragraph [0133]. Since the Office provided no explanation, Applicants are unsure, however, in which way the Office believes the use of a sample in the described assay is unclear. Paragraph [0133] describes a standard immunoassay that detects an analyte in a sample. In contrast to an assay of the invention, only one signal is recorded in the standard assay. By standard, the example means the assay generally or standardly used in the art. It appears that the Office may have mistakenly believed this assay used standards or controls, instead of a sample, which is not the case. "Sample" is the material which is presumed to contain the substance ("analyte") which is to be detected. The terms "analyte" and "sample" are defined in paragraphs [025] to [027] of the specification. Table 1 in paragraph [0134] of the specification shows the signal recordings of the standard assay (see the 5th column of the table). Applicants hope that this will clarify why a sample is used in the standard assay, and respectfully request that the objection is withdrawn.

Rejections under 35 U.S.C. § 112

Written Description

Claims 1-22 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Office Action, page 3. Specifically, the Office alleges that the amendments to claims 1 and 19 introduced new matter because the specification does not support "an 'L2-dependent' signal assigned to a time domain 'T2'." *Id.* Applicants respectfully traverse.

In the Reply to Office Action dated April 21, 2008, Applicants pointed, among others, to paragraph [012] as an example for sections of the specification that provide support for amended claims 1 and 19 (see page 13 of the Reply to Office Action). Paragraph [012] describes the method provided by the invention, which encompasses a one-step method, stating that "[t]he L1-dependent measurement signal is either determined chronologically separated from the L2-dependent or L1 plus L2-dependent measurement signal, or determined using another measurement method." (emphasis added). "Chronologically separated" in this context is synonymous to saying that the L1-dependent signal is determined at a different time point than the L2-dependent or L1 plus L2-dependent signal, and hence the method of the invention requires measurements at two different times, i.e. time T1 and time T2. It is clear from the specification that the method of the invention encompasses a single-step method. For example, paragraph [022] states that "[u]sing the method according to the invention, it is now possible to measure such analytes using the much faster single-step sandwich test rather than, as is customary, using a two-step sandwich test."

Support for amended claims 1 and 19 is also provided by paragraph [070] which describes the method of the invention, including a single-step method, wherein an L2-dependent signal is determined at time T2 (a time after T1). The described method includes a single-step method because all the antibody reagents are incubated with the sample simultaneously ("solid phase-R1, analyte ('A'; provided it is present in the sample), R2-L1 and R3-L2 (or R3-X) are mixed together and this incubation mixture is incubated until time T1"). The method includes two separate and subsequent measurements. The first is a measurement of an L1-dependent signal ("At time T1, the

measurement signal of the label L1 which is contained in the binding complex solid phase-R1-analyte-R2-L1 is determined"). The second is a measurement of a L2-dependent signal ("After that, i.e. at time T2, the measurement signal of the label L2 which is present in the binding complex solid phase-R1-analyte-R3-L2 (or -R3-X-Y-L2) is determined" (the underlining reflects the current amendment)).

In light of these remarks, Applicants respectfully submit that the specification supports the L2-dependent measurement signal at time T2 in independent claims 1 and 19, and Applicants therefore request that the rejection claims 1-22 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Definiteness

Claims 1-22 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Office Action, page 4. Applicants respectfully traverse.

Specifically, the Office alleged that the purpose of binding partner R3 which is associated with a label L2 (either directly or indirectly, such as via the specific binding pair X and Y) in the overall method is unclear. Office Action, page 4. Applicants point out that the claimed method requires the measurement of two signals. One signal is L1-dependent while the other signal is L2-dependent (see, for example, part (ii) of claim 1 or part (ii) of claim 19). As explained in detail in the specification (see, for example, paragraphs [012] to [015] and [018] for the conceptual basis and paragraphs [0134] and [0135] for the results of a specific example illustrating the concepts), both signals are required to detect, avoid or decrease a hook effect. The L2-associated binding partner

R3 does not "effectuate" a hook effect, as questioned by the Office, but rather it is required to detect, avoid or decrease a hook effect.

The Office further alleged that it is unclear how one determines a signal either at time T1 or at time T2. Office Action, pages 4-5. Applicants respectfully point to the specification, for example, paragraphs [012] to [015], for an explanation of the conceptual basis of the claimed method. It is important to note, for example, that "[t]he binding partners R2 and R3 are selected such that a saturation of the analyte A-binding sites of the R2 binding partners present in the incubation mixture takes place at a higher analyte A concentration and/or at a later time in the incubation than does the saturation of the analyte A-binding sites of the R3 binding partners which are present in the incubation mixture." See paragraph [012]. Thus, "[t]he L1-dependent measurement signal is either determined chronologically separated from the L2-dependent or L1 plus L2-dependent measurement signal, or determined using another measurement method." *Id.* It is clear to one skilled in the art that the exact timing conditions for the two measurements might have to be optimized for each specific combination of analyte, binding partners and labels used in the claimed method. The specification states as much in paragraph [015] (emphasis added):

> The method is based on the formation of the sandwich complexes R1-A-R2 and R1-A-R3 being affected to different extents by the hook effect: a decrease in the measurement signal occurs at a higher sample analyte concentration first in the case of the R1-A-R2 sandwich complex formation than in the case of the R1-A-R3 sandwich complex formation. <u>The skilled person can relatively simply determine the binding partners and reaction conditions which are suitable in each case</u> by first of all measuring the R1-A-R2 sandwich complex formation and the R1-A-R3 sandwich complex formation in separate test methods.

The Office further alleged that the phrase "determining [...] an L2-dependent measurement signal [...] using measurement method 2" is indefinite. Office Action, page 5. Applicants respectfully disagree because the specific instance cited by the Office (wherein L1 and L2 are the same label) is only one embodiment of the claimed method, and the specification does not limit the use of two different measurement methods for measuring L1-dependent and L2-dependent or L1 plus L2-dependent measurement signals to this specific embodiment. The claimed method can also use different measurement methods in instances when L1 and L2 are different labels. For example, paragraph [014] of the specification provides examples for such instances.

The Office further alleged that the phrase "determining [...] an L2-dependent measurement signal or an L1 plus L2-dependent measurement signal using measurement method 2" is indefinite. Office Action, page 5. Applicants respectfully disagree because the claims 1 and 19 encompass embodiments where label L1 and L2 are the same. Such an embodiment is disclosed, for example, in paragraph [058] of the specification. In such an instance, measurement method 2 detects not only L2 but L1 plus L2 ("the measurement signal of the chemiluminescer particles could be determined as label L2 plus L1 using a luminometer").

Finally, the Office alleged that step (iii) of claim 5 is indefinite in view of step (ii) of claim 1 because it is unclear how time T1 and time T2 are different in claim 5. Office Action, page 5. Applicants respectfully disagree. Part (iii) of claim 5 states that T1 is earlier than T2. Thus, T1 and T2 are different in claim 5 in that T1 is earlier than T2.

In light of these remarks, Applicants respectfully submit that claims 1-22 are definite, and Applicants therefore request that the rejection of claims 1-22 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1-3, 7, 9-12, 16 and 17 were rejected under 35 U.S.C. § 102(b) as being anticipated by Klein et al. The Office maintained this rejection from the previous Office Action, asserting again that Klein et al. describe a method comprising (1) incubating a sample with a binding partner associated with a solid phase, and binding partners associated with labels, wherein the binding partners have different affinity towards the analyte; and (2) determining analyte label-dependent signals using different methods at different times. Office Action, page 8. Applicants respectfully disagree for at least the same reasons presented in the Reply to Office Action dated April 21, 2008.

The Office alleges that "Binding ligand" in Figure 1 of Klein represents "binding partners associating with . . . a solid phase." Office Action, page 6. However, "Binding ligand" in Klein's Figure 1 is not associated with a solid phase. In Klein's Figure 1, only wheat germ agglutinin (WGA) is associated with a solid phase, the solid phase being controlled pore glass (CPG). See Klein et al., page 5336, second to last paragraph of column 2 ("As a model system..."). Furthermore, the "Binding ligand" referred to in Klein's Figure 1 does not represent a "binding partner" as required by the claims of the instant invention, because Klein's "Binding ligand" is neither associated with a solid phase, a label, or a member X of a specific binding pair, nor does it have binding sites for an analyte that is to be detected by the described NMR method. Rather, Klein's "Binding ligand" itself represents a substance in a sample that is to be detected by the

described NMR method. See Klein et al., Figure 1 legend ("A fast exchange equilibrium between receptor bound ligand and the free state allows the detection of these molecules in solution" (emphasis added)). Thus, "Binding ligand" in Klein's Figure 1 is more akin to an analyte to be detected in a sample than to a binding partner of such an analyte.

The Office further alleges that "Binding ligand" in Klein's Figure 1 also represents "binding partners associating with two labels." Office Action, page 6. However, for the reasons outlined above the "binding ligands" depicted in Klein's Figure 1 do not represent "binding partners" as required by the claims of the instant invention. In addition, the "binding ligands" depicted in Klein's Figure 1 are not associated with a label according to the instant invention. The Office asserted that a hydrogen atom is a label that is associated with the "binding ligands". Office Action, page 6. However, in Klein, the hydrogen atom is an integral component of the "Binding ligand" molecules. It is therefore not associated with the "binding ligands" as defined by the instant invention. See specification, paragraph [035].

The Office further alleges that WGA in Klein's Figure 1 represents an analyte towards which the "binding ligands" (as "binding partners") have different affinities. Office Action, page 6. However, WGA in Figure 1 does not represent an analyte as required by the claims of the instant invention. An analyte of the instant invention is a substance in a sample that is to be detected by the claimed methods. See specification, paragraph [025]. In contrast, WGA in Klein's Figure 1 is itself chemically coupled to a solid support, CPG (see also Scheme 1 on page 5337). The WGA in Klein does not function as an analyte. Instead, the WGA represents a means for detection.

The Office further alleges that Klein's Figure 2 shows the use of different methods for determining analyte label-dependent signals. Office Action, page 6. However, none of the methods used in Figure 2 detects WGA, which the Office contended represents the analyte. Rather, Klein's methods detect one or several of the oligosaccharides in the test solution. See Klein et al., page 5337, Figure 2 legend. The oligosaccharides analyzed in Klein's Figure 2 correspond to the "Binding ligand" in Figure 1.

In sum, the method described by Klein et al. represents a method to detect binding of a ligand (for example, a oligosaccharide as in Figure 2) to an immobilized receptor (for example, WGA coupled to CPG). The ligand may be analogous to an analyte of the instant invention in the sense that it is the subject of a detection method. The method of Klein et al. includes only <u>one</u> binding partner for the ligand, namely the immobilized receptor. The methods claimed in the instant invention require <u>three</u> different binding partners (R1, R2 and R3) for the analyte. Since the three binding partners are distinct elements of the claims, Klein et al. cannot anticipate the claims. To anticipate a claim, the reference must teach <u>every</u> element of the claim. MPEP § 2131.

The Office has repeated its rejection of claims 1-3, 7, 9-12, 16 and 17 as being anticipated by Klein et al., stating that Applicants' arguments have been carefully considered but have not been found persuasive. Office Action, page 7. However, the Office has failed to explain which aspect of Applicants' arguments was unpersuasive in the Office's opinion. The Office has not even provided a single example of how Applicants' arguments are thought to be faulty. Furthermore, the Office has again failed to explain how the method described in Klein et al. is believed by the Office to comprise

each and every element of the method in the rejected claims, including three different binding partners for the analyte. If the Office maintains this rejection again, Applicants respectfully request that the Office provide a scheme (for example, taking Figure 1 of Klein et al as a basis) that indicates exactly which component of the mixture used in the method described by Klein et al corresponds, in the Office's opinion, to each of the components required in the method of the rejected claims, including an analyte A (if present in the sample), a solid phase, an analyte A-specific binding partner R1 associated with the solid phase, an analyte A-specific binding partner R2 associated with label L1, and an analyte A-specific binding partner R3 associated with label L2.

In light of the above, Applicants respectfully submit that claims 1-3, 7, 9-12, 16 and 17 are not anticipated by Klein et al and request that their rejection under 35 U.S.C. § 102(b) be withdrawn.

Conclusion

Applicants respectfully request the Office to enter this Reply, and the reconsideration of the application and timely allowance of the pending claims.

Request for Interview

Should the Office maintain any rejection, Applicants request that the Examiner contact the undersigned at 202-408-4316 so that a suitable date and time can be scheduled for an Examiner interview to clarify any issues remaining in this case.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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